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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,691	SHEPARD ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/02 & 2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The specification has been amended by the preliminary amendment filed May 20, 2002.

Claims 1-24 have been canceled, and claims 25-31 have been added by the amendment filed Feb. 5, 2004.

Applicant has properly addressed the restriction requirement as it applies to the newly added clams.

In response to the restriction requirement, applicant has elected the subject matter of invention IA: *ex vivo* method of employing a wild type Rb gene encoding replication defective retrovirus vector to treat an autologous cell preparation for reinfusion into a tumor bearing patient.

Applicant mainly traverses on the basis *In re Weber, In re Haas I, In re Haas II,* and MPEP 803.02.

The traversal has been considered and is not found persuasive because as set forth in *In re Harnisch,* 206 USQP 300 (CCPA, 1980), the court considered *Weber, In re Haas I,* and *In re Haas II* fully, and states:

> Each case involving propriety of Markush groupings must be decided on its facts on case by case basis; Court of Customs and Patent Appeals adheres to holding in In re Weber, 198 USPQ 328, and In re Haas, 98 USPQ 334; unity of invention concept is not to be confused with "misjoinder" under 35 U.S.C. 121 rejection; "unity of invention" is appropriate term to apply where unrelated inventions are involved, that is, inventions that are truly independent and distinct.

Thus, § 121 provides the Commissioner with the authority to promulgate rules designed to restrict an application to one of several claimed inventions when those inventions are found to be "independent and distinct."

In this instance, the Rb gene is structurally and functionally distinct from the Wilms tumor suppressor gene WT1. As such, a search of a prior art that teaches the invention involving the use of the wild type Rb gene would not necessarily render the invention involving the WT1 gene anticipated or obvious.

As such, it would be unduly burdensome for the examiner to search and examine for each of the cited tumor suppressor gene's subject matter per filing fee. This point is further supported in *In re Harnisch,* where in the court states:

> Even though the statute allows the applicant to claim his invention as he sees fit, it is recognized that the PTO must have some means for controlling such administrative matters as examiner caseloads and the amount of searching done per filing fee.

Furthermore, the restriction letter does not set forth or imply a rejection under § 121. On the contrary, the restriction letter in fact states that generic or linking claims that embrace the restricted group will be examined by the examiner should a group be elected. The restriction letter states:

> Note that the restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), as listed above. Upon the allowance of the linking claims, the restriction requirement as to the liked invention shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such (claim(s) depending from or including all the limitations of the allowable lining claim(s) is/are presented in a continuation or divisional application, the claims or the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler,* 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Thus, applicant's citation of par. 331 from *In re Weber* is mischaracterized and

not found persuasive. Applicants claim the restricted groups here explicitly, and it is clear on the record that the linking claims embracing all of the restricted groups are not fragmented, and will be examined as a whole by the examiner.

Applicant's citation of page 334, which is simply an concurring opinion by Judge Rich and not a part of the main decision, has been considered, but is not found persuasive because the opinion does not represent the fact-patterns as set forth by precedent court decisions. On the contrary to applicant's assertion, the court decision in *In re Harnisch* states:

> Clearly our decision in *In re Hengehold*, 58 CCPA 1099, 440 F.2d 1395,169 USPQ 473 (1971), disposed of the theory that a restriction requirement and the subsequent action of the examiner in withdrawing nonelected claims from consideration, 9 per se, constitutes a rejection.

As such, applicant's citations of MPEP 803.02 and the court decisions from *In re Weber, In re Haas I,* and *In re Haas II* are not found persuasive.

Thus, the restriction remains proper, and thus, made final. The examiner further acknowledges that applicant has elected the group involving a retinoblastoma tumor suppressor gene, and leukemia as a tumor cell species. Applicant's claims, which claim specifically the subject matter of WT1 gene or colon carcinoma gene DCC have been have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

The specification is objected because the brief description of drawings does not contain proper reference to Figures 1A, 1B, Figures 3A-3C, and Figures 4A-4B as

depicted in the drawings. A change from a recitation of "Figure 4 shows" to – Figures 4A-4B show -- , for example, would obviate the objection.

The specification is also objected because this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because page 9 contains a polypeptide sequence comprising more than 4 amino acid resides. While a paper copy of the sequence listing together with the computer readable file have been entered, the polypeptide sequence as disclosed in the specification must contain a reference to SEQ identifier. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention can be reasonably construed as a method for purging human bone marrow cell preparation of tumor cells *ex vivo,* said method comprising subjecting a mixed population of blood cells or hematopoietic progenitor cells, and tumor cells to infection with a recombinant replication-incompetent retrovirus containing a nucleic acid encoding a tumor suppressor gene, which is generically claimed. The specification discloses the manufacture of replication-incompetent expression vectors encoding the p53 tumor suppressor gene and their use in tumor cell lines *in vitro.* The application discloses that transduced tumor cells containing the p53 gene when implanted into mice show a reduction of tumor formation (examples III-V, VII and VIII). Beside the focus of the p53 gene throughout the specification, the specification only discloses and claims that a tumor suppressor gene can be a wild-type retinoblastoma tumor suppressor gene (Rb gene), Wilms tumor suppressor gene WT1, or colon carcinoma DCC.

Such description does not appear to represent a genus of tumor suppressor genes, which are not linked by any substantially common structure by either the specification or the state of the prior art. The prior art of record such as Mastrangelo and Friedmann suggests that the list of putative tumor suppressor genes is large and growing. In analyzing whether the written description requirement is met for genus claim, it is first determined whether a representative number of species have been described by their complete structure. In this case, only genes of the disclosed species of wild type Rb gene, WT1, p53 and colon carcinoma gene DCC are mentioned by the as-filed specification. While it is apparent that the p53 and Rb genes are well

recognized in the prior art, there is no evidence the sequence structure of a wild type colon carcinoma DCC gene is available at the time of effective filing of this as-filed application. The lack of a sufficient description of the specific structures of a representative number of species of each of the respective claimed genus, would not support applicant's possession of genus claims. In other words, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims, requires more than a mere statement that it is part of the invention and a reference of just one disclosed species; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of polynucleotide sequences coding for a tumor suppressor gene product. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming a generic method, wherein a necessary requirement a generic tumor suppressor gene essential for the practice of the claimed invention, without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff

v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a representative numbers of species from each of the listed tumor types as claimed, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Even a mere disclosure of a probing strategy or plan for the identification and isolation of tissue specific tumor suppressor genes, which are yet to be discovered and available in the prior art without the complete nucleotide sequence of the sequences, which are deemed essential to the practice of the full breadth of the claimed invention, is not sufficient to demonstrate that Applicants were in possession of the claimed invention as recited in claims 19 and 23. Thus, it is not apparent to one skilled in the art as to how claims encompassing the use of a genus of tumor suppressor genes, find an adequate support from this instant disclosure at the time the invention was made.

In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 25-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of inhibiting the growth of tumor cells in an autologlous cell preparation for reinfusion into a tumor bearing patient, the method comprising contacting the cell preparation *ex vivo* with a recombinant replication-incompetent retrovirus containing a nucleic acid encoding a gene product of a wild type p53 gene or Rb gene, wherein the

cell preparation comprises a mixed population of tumor cells deficient in the expression of the wild type tumor suppressor p63 or Rb, does not reasonably provide enablement for any other scope, which embrace tumor suppressor genes other than Rb or p53, and/or other treating embodiments such as prevention and/or a complete purge of tumor cells from the preparation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Since the claimed invention is not supported by a sufficient written description (for possessing of the genus of polynucleotide sequences coding for a wild type tumor suppressor gene, which is essential to the practice of the claimed invention, particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention as broadly claimed so that it would operate as intended.

In addition to the above issue, the claimed invention can be reasonably construed as a method for purging human bone marrow cell preparation of tumor cells *ex vivo,* said method comprising subjecting a mixed population of bone marrow cells and tumor cells to infection with a recombinant replication-incompetent retrovirus containing a nucleic acid encoding a tumor suppressor gene. The specification discloses the manufacture of replication-incompetent expression vectors encoding the p53 tumor suppressor gene and their use in tumor cell lines *in vitro.* The application discloses that transduced tumor cells containing the p53 gene when implanted into mice show a reduction of tumor formation (examples III-V, VII and VIII). However, neither the

application nor the incorporated references have demonstrated that the claimed invention can be used to prevent the growth of tumor cells in the preparation or a complete purge of tumor cells present in a mixed population of tumor cells deficient in the expression of p53 and normal hematopoietic progenitor or blood cells. The state of the art reviewed by Mastrangelo *et al.* (Seminars in Oncology, 1996, vol. 23, 1:4-21) teaches that the introduction of the wild-type p53 gene into tumor cells *ex vivo* lacking a normal p53 gene only suppresses cell growth. Thus, it is not apparent as to how the suppressed cell growth can be reasonably extrapolated to any other treatment of an autologous cell preparation comprising normal blood cells and tumor cells.

The claims also encompass genes other than the p53 exemplified. However, there is no information provided as to the particular nucleic acid sequences, for example, nor is there any suggestion in the specification that the artisan could substitute a known tumor suppressor gene for the p53 gene in the working examples and could reasonably envision a success of a tumor cell growth inhibition for a broad genus of a variety of tumor suppressor genes, notwithstanding the lack of a written description of such genus. The Friedmann paper (Cancer Supplement, 1992, Vol. 70, No. 6) states

> That cancer suppression by a virally delivered gene is possible for the rb and p53 genes is no assurance that the same will be feasible for the other members of the rapidly growing family of tumor-suppressor genes. No similar tumor suppression results have been reported for other such genes. The phenomenon of suppression of tumorigenicity with a foreign gene depends on the function encoded by the gene and the role that gene plays in determining replication and differentiation processes in the cell. In some cancer cells, some cancer-suppressor functions probably are less important than other functions in determining the aberrant phenotype. Therefore, genetic transfer probably would be ineffective in altering the aberrant properties (p. 1814).

Thus, the extrapolation of applicants' results to any tumor suppressor gene is not

recognized in the art, and thus, not considered to be conventional or routine by a skilled artisan at the effective filing date of this instant application. The showing of decreased tumor size does appear to be co-relatable to the full breadth of the claims, particularly in view of the reasons set forth above.

It is therefore concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of co-relatable working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for one skilled in the art to practice the invention.

Claims 25-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25, and claims dependent there from, are indefinite in the recitation of "the hyperproliferative phenotype", because not all tumor cells deficient in a particular wild type gene are hyperproliferating in the same manner. As such, the term lacks a proper antecedent basis.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or

described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25-27 are rejected under 35 U.S.C. 102(a) as being anticipated by Cheng *et al.* (Cancer Res., 52, 222-226, 1992).

The Cheng *et al.* reference discloses the transduction of human T-cell acute lymphoblastic leukeumia (T-ALL) cell lines with retroviral vectors encoding the wild-type 53 gene, and suppression of the neoplastic phenotype as measured by criteria including

morphology, colony formation in soft agar, and abrogated tumorigenicity in nude mice. Cheng *et al.* further disclose that "acute leukeumia cell suppression via high-efficiency infection with retroviruses encoding wtp53 may be feasible and beneficial in T-ALL cases as part of a bone marrow transplantation regimen in an effort to reduce the frequency of post transplantation relapse" (p. 222).

Claims 25-27, and 30 are rejected under 35 U.S.C. 103 as being unpatentable over Huang *et al.* (Science, Vol. 242, 1988, pages 1563-1566) in view of Cheng *et al.* (Cancer Res., 52, 222-226, 1992).

The Huang *et al.* reference discloses the transduction of cell lines with retroviral vectors encoding the RB gene, and suppression of the neoplastic phenotype as measured by criteria including morphology, growth rate and saturation density in culture, colony formation in soft agar, and tumorigenicity in nude mice. Huang *et al.* further disclose that "replacement of suppressor genes in tumor cells, as demonstrated here, could be a novel strategy for the treatment of clinical malignancy...Therapy may not need to be targeted because cancer suppressor genes should not harm normal cells" (p. 1566). Here, it would have been obvious to one of ordinary skill in the art to have employed the method of purging a mixed population of bone marrow cell preparation of tumor cells by using a transduced retroviral vector containing the wild-type Rb gene since Cheng *et al.* teach that acute leukeumia cell suppression via high-efficiency infection with retroviruses encoding a tumor suppressor gene may be feasible and beneficial in T-ALL cases as part of a bone marrow transplantation regimen in an

effort to reduce the frequency of post transplantation relapse, as indicated above. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 25-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,438,352. Although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims are drawn to a method of inhibiting a tumor cell phenotype of tumor cells deficient in expression of endogenous wild-type p53 protein, wherein the method comprises contacting a mixed population comprising the tumor cells and hematopoietic progenitor cells *ex vivo,* in the absence of selection for

retroviral infection, with a recombinant replication incompetent retrovirus containing a nucleic acid that encodes a tumor suppressor p53 gene product.

Thus, both sets of claims are obvious variant of one another.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0184.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER